AMENDMENTS TO THE SPECIFICATION

At page 8, line 1, insert:

The present inventive adenoviral vector includes a spacer to provide viral growth in a complementing cell line similar to that achieved by singly replication deficient adenoviral vectors, particularly a singly replication deficient E1 deficient adenoviral vector. In the preferred E4$^-$ adenoviral vector of the present invention wherein the L5 fiber region is retained, the spacer is desirably located between the L5 fiber region and the right-side ITR. More preferably in such an adenoviral vector, the E4 polyadenylation sequence alone or, most preferably, in combination with another sequence exists between the L5 fiber region and the right-side ITR, so as to sufficiently separate the retained L5 fiber region from the right-side ITR, such that viral production of such a vector approaches that of a singly replication deficient adenoviral vector, particularly a singly replication deficient E1 deficient adenoviral vector.

In the absence of a spacer, production of fiber protein and/or viral growth of the multiply replication deficient adenoviral vector is reduced by comparison to that of a singly replication deficient adenoviral vector. However, inclusion of the spacer in at least one of the deficient adenoviral regions, preferably the E4 region, counteracts this defect in growth and fiber expression.

The function of the replication deficient region is provided by a complementing cell line. As a result, the spacer does not need to provide the deficient function and can be any sequence, limited only by the size of the insert that the vector will accommodate. The spacer alone can function to repair the growth defect and decreased fiber expression found in multiply replication deficient adenoviral vectors. The spacer can be of any suitable size, desirably at least about 15 base pairs (e.g., between about 15 base pairs and about 12,000 base pairs), preferably about 100 base pairs to about 10,000 base pairs, more preferably about 500 base pairs to about 8,000 base pairs, even more preferably about 1,500 base pairs to about 6,000 base pairs, and most preferably about 2,000 to about 3,000 base pairs.

The spacer can contain any sequence or sequences which are of the desired length. The spacer sequence can be coding or non-coding and native or non-native with respect to the adenoviral genome, but does not restore the replication function to the deficient region. The spacer can also contain a promoter-variable expression cassette. More preferably, the spacer comprises an additional polyadenylation sequence and/or a passenger gene. Preferably, in the case of a spacer inserted into a region deficient for E4, both the E4 polyadenylation sequence and the E4 promoter of the adenoviral genome or any other (cellular or viral) promoter

remain in the vector. The spacer is located between the E4 polyadenylation site and the E4 promoter, or, if the E4 promotor is not present in the vector, the spacer is proximal to the right-side ITR.

The spacer can comprise any suitable polyadenylation sequence. Examples of suitable polyadenylation sequences include synthetic optimized sequences, BGH (Bovine Growth Hormone), polyoma virus, TK (Thymidine Kinase), EBV (Epstein Barr Virus) and the papillomaviruses, including human papillomaviruses and BPV (Bovine Papilloma Virus). Preferably, particularly in the E4 deficient region, the spacer includes an SV40 polyadenylation sequence. The SV40 polyadenylation sequence allows for higher virus production levels of multiply replication deficient adenoviral vectors.

Although a passenger gene is typically inserted into the E1 deficient region of an adenoviral genome, a passenger gene can also function as the spacer in the E4 deficient region of the adenoviral genome. The passenger gene is limited only by the size of the fragment the vector can accommodate and can be any suitable gene. Examples of suitable passenger genes include marker gene sequences such as pGUS, secretory alkaline phosphatase, luciferase, B-galactosidase, and human anti-trypsin; therapeutic genes of interest such as the cystic fibrosis transmembrane regulator gene (CFTR); and potential immune modifiers such as B3-19K, E3-14.7, ICP47, fas ligand gene, and CTLA4 gene.